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Aluminium exposure and toxicity: From environmental sources and absorption to molecular mechanisms and organ specific effects A comprehensive review

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Abstract
Aluminium (Al) is one of the most abundant elements in the Earth's crust and is widely used in industrial, food, pharmaceutical, household, and personal-care applications. As a result, humans are exposed to aluminium through a variety of environmental and occupational sources, including food, drinking water, inhalation of aluminium-containing dust and fumes, and consumer products. The extent of aluminium absorption and distribution depends on factors such as the chemical form, route and level of exposure, duration of exposure, and physiological conditions. Once absorbed, aluminium can be distributed to several tissues, including the brain, liver, kidneys, bones, and reproductive organs. Its toxic effects have been linked to interconnected cellular disturbances involving oxidative stress, impaired antioxidant defence, mitochondrial dysfunction, altered enzyme activity, disruption of cellular signalling, inflammation, and apoptosis. Experimental studies have reported biochemical, molecular, and histopathological changes in several organ systems, including the nervous, hepatic, renal, respiratory, reproductive, and endocrine systems. In this review, we summarize the major sources and routes of aluminium exposure, its absorption and distribution, and the mechanisms that contribute to aluminium-induced toxicity. Particular attention is given to organ-specific effects and the role of oxidative stress in tissue injury. The review also discusses limitations in the existing evidence, including differences between experimental exposure conditions and human exposure, and identifies areas requiring further investigation. A better understanding of these factors is important for assessing the potential health risks associated with aluminium exposure.

Keywords: Aluminium toxicity, Oxidative stress, Organ-specific toxicity, Hepatotoxicity, Nephrotoxicity, Neurotoxicity, Environmental exposure

Introduction

Aluminium (Al) is the third most abundant element in the Earth's crust and is extensively used in industrial, food, pharmaceutical, household, and personal-care applications (Klotz *et al*., 2017; Stahl *et al*., 2018) [30, 49]. Its widespread occurrence and diverse applications provide multiple opportunities for human and environmental exposure. Although aluminium has no established essential biological function in humans, prolonged or excessive exposure can result in tissue accumulation and may interfere with normal cellular and physiological processes (Yokel, 2012) [59]. Experimental and observational evidence has associated aluminium exposure with adverse effects involving several organ systems, particularly the nervous system, liver, kidneys, skeletal system, respiratory system, and reproductive organs (Bonfiglio *et al*., 2023) [5].

Human exposure to aluminium occurs through several routes, with ingestion and inhalation being particularly important. Dietary intake can contribute substantially to overall exposure because aluminium may be naturally present in food or may be introduced during food processing through additives and food-contact materials (Stahl *et al*., 2011; Stahl *et al*., 2018. [49] Drinking water can also contribute to aluminium exposure, depending on its natural occurrence and the conditions associated with water treatment (Klotz *et al*., 2017; Bhatnagar and Gupta, 2021) [4, 30]. Additional exposure may arise from aluminium-containing pharmaceutical preparations and personal-care products. The contribution of dermal exposure to systemic aluminium burden, however, appears to depend on the formulation and conditions of use (Kumar and Rao, 2021) [31]. Occupational exposure is of particular concern in activities involving aluminium processing, smelting, welding, and the generation of aluminium-containing dust and fumes (Wesdock & Arnold, 2014; Choupani *et al*., 2018; Hadrup *et al*., 2024) [9, 25, 56].

Once absorbed, aluminium enters the circulation and can be distributed to different tissues, including the bone, liver, kidneys, and brain (Klotz *et al*., 2017; Yokel, 2012; Sieg *et al*., 2019) [30, 46, 59]. However, aluminium absorption is relatively complex and is influenced by factors such as its chemical form, exposure route, dose, duration of exposure, and physiological conditions. In the gastrointestinal tract, dietary constituents and chemical interactions can modify aluminium bioavailability. For example, citrate has been reported to enhance aluminium uptake by forming soluble aluminium complexes, whereas phosphate can reduce absorption (Slanina *et al*., 1984; DeVoto & Yokel, 1994) [14, 48]. Inhalation provides an additional pathway for systemic exposure, particularly in occupational settings, where the characteristics and composition of airborne aluminium-containing particles can influence their biological effects (Wesdock & Arnold, 2014; Hadrup *et al*., 2024) [25, 56].

The biological effects of aluminium are not attributable to a single mechanism. Instead, its toxicity involves several interconnected cellular and molecular processes (Cheng *et al*., 2021) [8]. Oxidative stress is one of the most frequently reported features of aluminium exposure and may arise from increased reactive oxygen species generation together with disruption of antioxidant defence systems (Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46]. Persistent oxidative imbalance can promote lipid peroxidation and oxidative

modification of proteins and nucleic acids, thereby contributing to cellular dysfunction. Aluminium exposure has also been associated with mitochondrial dysfunction, altered enzyme activity, disturbances in intracellular signalling and calcium homeostasis, inflammatory responses, and activation of cell-death pathways (Sieg *et al*., 2019; Walton, 2012) [46, 54]. The relative importance of these mechanisms may differ among tissues and can be influenced by aluminium species, exposure route, dose, duration, and experimental conditions.

Although a substantial body of research has examined aluminium toxicity, the available evidence remains fragmented across different aluminium compounds, exposure scenarios, experimental models, and target organs. Findings obtained using different doses and routes of administration are not always directly comparable, particularly when attempting to relate experimental exposure to realistic human exposure. Therefore, an integrated view of aluminium toxicity that connects environmental and occupational sources with absorption, tissue distribution, molecular mechanisms, and organ-specific injury is warranted. The present review synthesizes evidence on the major sources and routes of aluminium exposure, its absorption and distribution, the cellular and molecular mechanisms underlying its toxicity, and its effects on major organ systems. Particular attention is given to the interconnected nature of oxidative stress, mitochondrial dysfunction, inflammation, altered signalling, and apoptosis, while important limitations and evidence gaps relevant to long-term and human exposure are also considered.

Sources and Environmental Exposure to Aluminium

Aluminium is widely distributed in the environment and occurs naturally in soil, rocks, water, and minerals. In addition to these natural sources, human activities and the extensive use of aluminium-containing materials and compounds contribute substantially to environmental and human exposure. The major sources of aluminium exposure can be broadly classified into natural, industrial and occupational, and consumer-related sources (Klotz *et al*., 2017; Stahl *et al*., 2018) [30, 49].

1. Natural Sources

Soil represents an important natural reservoir of aluminium. Its availability and mobility are strongly influenced by soil pH and chemical composition. Under acidic conditions, aluminium becomes more soluble, increasing the availability of potentially phytotoxic aluminium species, particularly Al^{3+}. Soil acidity can therefore influence the uptake and accumulation of aluminium by plants (Ofoe *et al*., 2023) [38].

Aluminium can subsequently enter the food chain through its presence in plants grown in aluminium-containing soils. The concentration of aluminium in vegetables and other plant-derived foods may vary according to soil characteristics, environmental conditions, and plant species (Ofoe *et al*., 2023; Ghasemidehkordi *et al*., 2018) [23, 38]. Consequently, regions with greater aluminium availability in soil may contribute to increased aluminium accumulation in edible plant tissues (Ghasemidehkordi *et al*., 2018) [23].

Water is another environmental source of aluminium. Naturally occurring aluminium may enter water through the weathering and dissolution of aluminium-containing minerals and rocks. Anthropogenic activities, including mining and industrial processes, may further contribute to aluminium contamination of aquatic environments. Aluminium concentrations in water are also influenced by pH because changes in acidity can alter its solubility and chemical speciation (Scancar & Milacic, 2006) [44].

Aluminium is abundant in rocks and minerals, particularly in aluminium-rich materials such as bauxite and feldspar. Chemical weathering of these minerals can release aluminium into soil and water, while rainfall and acidic conditions may influence its subsequent movement through terrestrial and aquatic systems (Drever & Stillings, 1997; Li *et al*., 2026) [16].

Atmospheric aluminium may also originate from natural processes such as soil and rock weathering. Atmospheric concentrations can increase in urban and industrial environments because of anthropogenic activities, including industrial emissions, construction, and other processes that generate aluminium-containing dust and particulate matter (Alasfar & Isaifan, 2021) [2].

2. Industrial and Occupational Exposure

Industrial activities represent an important anthropogenic source of aluminium exposure. Mining, refining, smelting, casting, welding, and other aluminium-processing operations may generate aluminium-containing dust, fumes, and particulate matter. Workers involved in these activities may therefore experience occupational exposure, particularly through inhalation (Wesdock & Arnold, 2014; Choupani *et al*., 2018) [9, 56].

Exposure during aluminium mining and refining may occur through inhalation of bauxite- and alumina-containing dust. Aluminium smelting and related industrial operations may additionally expose workers to complex mixtures of particulate matter and other combustion-related substances. The toxicological effects of occupational exposure depend on the composition and concentration of airborne materials, particle characteristics, duration of exposure, and workplace conditions (Wesdock & Arnold, 2014; Hadrup *et al*., 2024) [25, 56].

Evidence from occupational studies indicates that aluminium exposure can be reflected in biological monitoring parameters such as urinary aluminium concentrations. Workers experiencing higher occupational exposure have been reported to exhibit increased urinary aluminium levels compared with individuals exposed to lower concentrations (Choupani *et al*., 2018; Hadrup *et al*., 2024) [9, 25].

Inhalation is particularly relevant because aluminium-containing particles can reach the respiratory tract and, depending on particle characteristics and exposure conditions, may contribute to local pulmonary effects. Occupational exposure to aluminium-containing dust has been associated with respiratory effects and pulmonary toxicity (Dekali *et al*., 2022) [13].

3. Consumer-Related Sources

Aluminium exposure can also occur through commonly used consumer products. Food and beverages, pharmaceutical preparations, cosmetics, personal-care products, packaging materials, and aluminium cookware can all contribute to human exposure. Dietary exposure is particularly relevant because aluminium may be present naturally in food or may be introduced during processing through aluminium-containing additives and food-contact

materials (Klotz *et al*., 2017; Stahl *et al*., 2011; Stahl *et al*., 2018) [30, 49, 50].

Aluminium-containing food additives can increase the aluminium content of processed foods. In addition, contact between food and aluminium utensils or foil may facilitate aluminium transfer, particularly under conditions involving acidic or salty foods and elevated temperatures. Therefore, food preparation and storage practices may influence dietary aluminium exposure (Stahl *et al*., 2018; Shukla *et al*., 2023) [45, 49].

Pharmaceutical products represent another potential source of aluminium exposure. Aluminium compounds are used in certain antacid preparations and other pharmaceutical formulations, and repeated or prolonged use of aluminium-containing preparations may contribute to overall aluminium intake (Klotz *et al*., 2017) [30].

Personal-care and cosmetic products may also contain aluminium compounds, including certain antiperspirant and cosmetic formulations (Kumar and Rao, 2021) [31]. However, the extent to which aluminium from these products contributes to systemic exposure depends on the formulation, route of application, frequency of use, and degree of dermal penetration (de Ligt *et al*., 2022) [35].

Aluminium-containing packaging materials can provide an additional source of exposure. Under particular chemical and thermal conditions, aluminium may migrate from packaging into the material or product in contact with it. This is especially relevant under acidic conditions and elevated temperatures (Shukla *et al*., 2023; Stahl *et al*., 2018) [45, 49].

Routes of Exposure, Absorption and Distribution of Aluminium

The extent and biological consequences of aluminium exposure depend not only on the amount encountered but also on the route through which it enters the body. Following exposure, aluminium undergoes absorption, transport through the circulation, and distribution among different tissues. The gastrointestinal and respiratory systems represent the major routes of systemic exposure, while the nasal route has also been proposed as a potential pathway for aluminium delivery to the central nervous system. Factors such as aluminium speciation, pH, chemical complexation, dose, duration of exposure, and physiological conditions can influence its absorption and subsequent tissue distribution (Klotz *et al*., 2017; Yokel, 2012; Hadrup *et al*., 2024) [25, 30, 59].

1. Gastrointestinal Absorption

The gastrointestinal (GI) tract represents an important route of aluminium entry into the body, particularly following consumption of aluminium-containing food, water, and pharmaceutical preparations. However, only a small fraction of ingested aluminium is normally absorbed systemically, and the extent of absorption is strongly influenced by its chemical form and the conditions within the gastrointestinal tract (DeVoto & Yokel, 1994; Yokel, 2001) [14, 61]. Aluminium absorption is influenced by luminal pH, ligand binding, complexation, and interactions with dietary and physiological factors (DeVoto & Yokel, 1994) [14].

The bioavailability of aluminium is also affected by interactions with dietary components. Phosphate can reduce aluminium absorption, whereas citrate and other organic acids can enhance aluminium uptake by forming more soluble aluminium complexes (Slanina *et al*., 1984; DeVoto & Yokel, 1994) [14, 48]. Human experimental studies have also demonstrated enhanced gastrointestinal absorption in the presence of citrate (Priest *et al*., 2004) [41]. These findings indicate that the chemical environment in the gastrointestinal tract can substantially influence the fraction of aluminium that becomes systemically available.

Experimental studies have suggested that aluminium uptake across the intestinal epithelium may involve both transcellular and paracellular pathways, although the relative contribution of these mechanisms appears to depend on aluminium speciation and experimental conditions (Provan & Yokel, 1988; Jeong *et al*., 2020) [29, 43]. Interactions with essential minerals such as calcium and iron may also modify aluminium absorption, while physiological factors including age, mineral status, and renal function can influence aluminium disposition (DeVoto & Yokel, 1994; Drüeke *et al*., 2002) [14, 17].

Age and physiological condition may further influence gastrointestinal aluminium absorption. This consideration is particularly relevant in populations with altered gastrointestinal or renal physiology, including infants and individuals with impaired renal function (van der Voet, 1992; Corkins *et al*., 2019) [10, 52]. Overall, available evidence indicates that gastrointestinal aluminium absorption is governed by multiple interacting chemical, dietary, and physiological factors rather than by ingested dose alone (Klotz *et al*., 2017; DeVoto & Yokel, 1994) [14, 30].

2. Inhalation and Respiratory Exposure

Inhalation represents an important route of aluminium exposure, particularly in occupational environments where workers may encounter aluminium-containing dust, fumes, fibres, or particulate matter. Aluminium mining, smelting, welding, casting, and other industrial operations can generate airborne aluminium-containing materials (Wesdock & Arnold, 2014; Hadrup *et al*., 2024) [25, 56]. The respiratory consequences of exposure depend on factors including particle characteristics, concentration, duration of exposure, and the chemical composition of the inhaled material (Hadrup *et al*., 2024) [25].

Following inhalation, aluminium-containing particles may be deposited within different regions of the respiratory tract, depending on their aerodynamic properties and other particle characteristics. Experimental and occupational evidence indicates that some aluminium-containing materials can persist within pulmonary tissues and may induce local inflammatory or fibrotic responses under particular exposure conditions (Hadrup *et al*., 2024) [25].

Occupational biomonitoring studies have demonstrated that aluminium exposure can be reflected in urinary aluminium concentrations. Workers experiencing higher occupational exposure may exhibit higher urinary aluminium concentrations than individuals with lower exposure (Choupani *et al*., 2018; Hadrup *et al*., 2024) [9, 25]. The relationship between inhaled aluminium and systemic aluminium burden, however, depends on the physicochemical properties of the inhaled material and the efficiency of pulmonary clearance and absorption (El-Sayed *et al*., 2016) [19].

Aluminium-containing nanoparticles represent another potential form of inhalation exposure. Their small size and large surface area may influence pulmonary deposition,

cellular interactions, and clearance. However, the toxicological properties of nanoscale aluminium-containing materials cannot necessarily be extrapolated from those of conventional aluminium dust, and particle composition, solubility, surface characteristics, and experimental exposure conditions must be considered separately (Hadrup *et al*., 2024) [25].

3. Blood–Brain Barrier and Brain Penetration

The central nervous system represents an important target of aluminium exposure. Following systemic absorption, aluminium can reach the brain, although the fraction entering neural tissue is relatively small and depends on its chemical form, plasma speciation, exposure conditions, and physiological factors (Yokel, 2002; Yokel, 2006) [58]. The blood–brain barrier (BBB) is formed primarily by specialized endothelial cells joined by tight junctions and supported by pericytes and astrocytic end-feet, thereby providing a highly selective interface between the circulation and neural tissue (Sweeney *et al*., 2018; Profaci *et al*., 2020) [42, 51].

Experimental studies have demonstrated that aluminium introduced into the systemic circulation can subsequently be detected within brain tissues. Aluminium transport across the BBB may involve several processes, including movement of aluminium bound to low-molecular-weight ligands and interactions with transport systems associated with metal-binding proteins such as transferrin (Yokel, 2000; Yokel, 2002) [57, 58]. However, the precise mechanisms governing aluminium entry into and removal from the brain remain incompletely characterized.

The ability of aluminium to reach neural tissue is particularly relevant because prolonged cerebral retention may expose neural cells to oxidative, inflammatory, and cellular disturbances. Aluminium has been detected in different regions of the brain following experimental exposure, although the magnitude of accumulation varies according to dose, chemical form, route of administration, and duration of exposure (Yokel, 2002; Yokel, 2006) [58]. Thus, evidence for brain penetration supports the biological plausibility of neurological effects, but the relationship between environmental aluminium exposure and specific human neurological diseases remains an area of continuing investigation (Bonfiglio *et al*., 2023) [5].

4. Nasal and Olfactory Pathway

The nasal cavity represents another potential pathway through which inhaled aluminium-containing materials may interact with the central nervous system. The olfactory region provides anatomical access to the brain through olfactory neurons, and this pathway has been investigated for several environmental and pharmaceutical substances (Yokel, 2006).

Experimental studies have reported aluminium in the olfactory bulb and other neural tissues following nasal or intranasal exposure to aluminium-containing materials (Yokel, 2006; Kwon *et al*., 2013; Zatta *et al*., 1993) [33, 62]. These observations suggest that the olfactory pathway may contribute to aluminium delivery to the central nervous system under specific exposure conditions. However, the quantitative importance of this pathway in humans remains uncertain, particularly for typical environmental and occupational exposures.

The contribution of the nasal route may depend on the physicochemical characteristics of the aluminium compound or particle, exposure concentration, particle size, deposition pattern, and integrity of the nasal epithelium (Chalansonnet *et al*., 2018; Gänger & Schindowski, 2018) [7, 21]. Therefore, although the olfactory pathway represents a biologically plausible route of aluminium entry into the nervous system, its relative importance compared with systemic transport across the BBB requires further investigation.

5. Distribution and Tissue Accumulation

Following absorption, aluminium is transported through the bloodstream and distributed to several tissues. The liver and kidneys are particularly relevant to aluminium disposition because of their roles in metabolism, tissue handling, and elimination. Aluminium has also been detected in bone and brain tissue, where prolonged retention may contribute to tissue-specific effects (Klotz *et al*., 2017; Yokel & McNamara, 2001; Sieg *et al*., 2019) [30, 46, 61].

The liver can accumulate aluminium following exposure. Experimental studies examining aluminium distribution among hepatic subcellular fractions have demonstrated hepatic accumulation and changes in the distribution of aluminium among cellular components, suggesting that the liver participates in the handling and retention of absorbed aluminium (Van der Voet *et al*., 1992; Sieg *et al*., 2019) [46, 52].

The kidneys are another important site in aluminium disposition because renal excretion represents a major pathway for elimination of absorbed aluminium. Prolonged exposure or impaired renal function can increase systemic aluminium retention and may increase the aluminium burden in renal tissues (Yokel & McNamara, 2001; Klotz *et al*., 2017) [30, 61]. Consequently, renal function is an important determinant of aluminium toxicokinetics and potential accumulation.

Bone may act as an important long-term reservoir for aluminium, allowing the element to persist in the body for extended periods (Klotz *et al*., 2017; Yokel & McNamara, 2001) [30, 61]. Aluminium retention in bone has been associated with disturbances in bone mineralization in experimental and clinical settings. The prolonged retention of aluminium in tissues highlights the importance of both exposure duration and elimination capacity in determining its potential biological effects (Klotz *et al*., 2017; Mitra *et al*., 2021) [30, 37].

Molecular and Cellular Mechanisms of Aluminium Toxicity

Aluminium toxicity is a multifactorial process involving several interconnected molecular and cellular disturbances rather than a single toxicological pathway. Depending on its chemical form, concentration, exposure duration, and target tissue, aluminium may interfere with redox homeostasis, mitochondrial function, intracellular calcium regulation, membrane-associated signalling, inflammatory pathways, and cell survival mechanisms. These processes can interact with one another, resulting in progressive cellular dysfunction and tissue injury (Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46].

1. Oxidative Stress and Reactive Oxygen Species

Oxidative stress is one of the most consistently reported cellular responses to aluminium exposure. Aluminium can

disturb the balance between reactive oxygen species (ROS) generation and antioxidant defence, resulting in oxidative damage to cellular macromolecules (Cheng *et al*., 2021; Sieg *et al*., 2019) [8, 46]. Although aluminium itself is not a classical redox-active transition metal, it can promote oxidative imbalance indirectly through interactions with cellular antioxidant systems, iron homeostasis, mitochondrial function, and other metabolic processes (Klotz *et al*., 2017) [30].

Increased ROS production can promote lipid peroxidation, protein oxidation, and oxidative damage to nucleic acids. Experimental studies have reported alterations in antioxidant enzymes, including superoxide dismutase, catalase, and glutathione-dependent defence systems, following aluminium exposure (Sieg *et al*., 2019) [46]. Excessive lipid peroxidation may compromise membrane integrity and alter the function of membrane-associated proteins and signalling systems.

Oxidative stress may also amplify other mechanisms of aluminium toxicity. Persistent ROS generation can impair mitochondrial function, activate inflammatory signalling, alter intracellular calcium homeostasis, and promote cell-death pathways. Thus, oxidative stress may function both as an early cellular response and as a mediator that contributes to the progression of aluminium-induced tissue injury (Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46].

2. Mitochondrial Dysfunction

Mitochondria are important targets of aluminium-induced cellular injury because of their central role in energy production, redox regulation, and cell survival. Aluminium exposure has been associated with impaired mitochondrial bioenergetics, altered membrane function, and increased oxidative damage, particularly in experimental models of neurotoxicity (Sharma & Mishra, 2012).

Mitochondrial dysfunction may reduce ATP production while simultaneously increasing oxidative stress. Excessive mitochondrial ROS can further damage mitochondrial proteins, lipids, and nucleic acids, thereby establishing a cycle of oxidative injury and declining mitochondrial function. Such disturbances can impair energy-dependent cellular processes and increase cellular susceptibility to additional stressors (Kumar & Gill, 2014) [32].

The relationship between oxidative stress and mitochondrial dysfunction is therefore potentially bidirectional. Aluminium-induced oxidative imbalance can impair mitochondrial components, whereas damaged mitochondria may become an additional source of ROS. This interaction may be particularly important in tissues with high metabolic demands, such as the brain, liver, and kidneys.

3. Disturbance of Calcium Homeostasis and Intracellular Signalling

Aluminium can interfere with intracellular calcium homeostasis and calcium-dependent signalling pathways. Calcium ions act as important second messengers involved in neuronal transmission, muscle contraction, enzyme regulation, gene expression, and cell survival. Disruption of intracellular calcium regulation can therefore have widespread consequences for cellular function (Torre *et al*., 2018; Walton, 2012) [12, 54].

Experimental studies have demonstrated that aluminium exposure can alter calcium-dependent processes, including Ca^{2+}-ATPase activity and intracellular calcium concentrations. In rat neuronal preparations, aluminium exposure was associated with increased intracellular calcium, reduced Ca^{2+}-ATPase activity, and alterations in calcium-regulatory proteins (Martinez *et al*., 2017) [36]. More recent experimental evidence has also demonstrated direct effects of Al^{3+} on calcium pumps, including plasma-membrane and sarcoplasmic-reticulum Ca^{2+}-ATPases (Haug *et al*., 1994) [26].

Aluminium may additionally interfere with phosphoinositide-mediated signalling. Experimental evidence indicates that aluminium can alter inositol phosphate metabolism and intracellular Ca^{2+} signalling, thereby affecting receptor-mediated signal transduction (Gonzalez *et al*., 1994). Such disturbances may influence downstream pathways involved in cellular metabolism, proliferation, differentiation, and survival.

Importantly, the effects of aluminium on signalling may depend on its chemical species and the cellular environment. Aluminium complexes with different ligands can exhibit different biological activities, indicating that aluminium speciation should be considered when interpreting mechanistic toxicology studies (Walton, 2012) [54].

4. Enzyme Dysfunction and Altered Cellular Metabolism

Aluminium can interact with biological molecules and interfere with enzyme activity and cellular metabolism. Because Al^{3+} has a high affinity for oxygen-containing ligands, it can interact with phosphate-containing molecules and compete with biologically important metal ions in some biochemical systems. Such interactions may alter the activity of enzymes, transport proteins, and other cellular components (Walton, 2012) [54].

Aluminium exposure has also been associated with disturbances in cellular metabolic processes and energy homeostasis. Changes in enzyme activity may contribute to impaired antioxidant defence, altered intermediary metabolism, and reduced cellular capacity to respond to oxidative stress. The magnitude and direction of these effects depend on aluminium speciation, dose, exposure duration, and tissue type.

In addition, aluminium-induced changes in calcium signalling and membrane-associated processes can indirectly influence enzyme-regulated pathways. Therefore, enzyme dysfunction should not be considered an isolated mechanism but rather as part of the broader network of biochemical disturbances produced by aluminium exposure.

5. Membrane Perturbation and Signal Transduction

Cellular membranes represent another potential target of aluminium toxicity. Aluminium can interact with membrane-associated phospholipids and alter the activity of signalling components associated with the plasma membrane. Experimental evidence has demonstrated interactions between aluminium and phosphoinositide-associated membrane components, suggesting that membrane perturbation may contribute to altered intracellular signalling (Platt *et al*., 2001) [40].

Changes in membrane composition and lipid peroxidation can modify membrane fluidity, receptor function, ion transport, and intracellular communication. These alterations may subsequently affect calcium signalling and other second-messenger systems. Because membrane-associated pathways regulate multiple cellular processes,

their disruption may contribute to the diverse biological effects observed following aluminium exposure.

The extent of membrane perturbation is likely to depend on aluminium concentration, chemical form, membrane composition, and the presence of competing ligands. Therefore, findings obtained under high experimental aluminium concentrations should be interpreted cautiously when considering environmental exposure.

6. Inflammatory Responses

Inflammation represents another important component of aluminium-induced cellular injury. Aluminium exposure has been associated with activation of inflammatory responses and alterations in pro-inflammatory mediators in experimental models (Geetha & Jain, 2017) [22]. Oxidative stress may contribute to inflammatory signalling by activating stress-responsive pathways and promoting the release of inflammatory mediators.

In the nervous system, aluminium exposure has been associated with activation of glial cells and changes in inflammatory responses. Experimental studies have reported increased astrocytic and microglial activation together with oxidative stress following aluminium exposure (Akinrinade *et al*., 2015) [3]. These responses may contribute to a local inflammatory environment capable of amplifying neuronal and tissue injury.

Inflammation and oxidative stress can therefore reinforce one another. ROS may activate inflammatory pathways, while inflammatory cells and mediators can generate additional oxidative stress. This reciprocal interaction provides a possible mechanistic link between persistent aluminium exposure and chronic tissue dysfunction (Igbokwe *et al*., 2020; Campbell, 2002) [6].

7. Genotoxicity and DNA Damage

Experimental studies have investigated DNA damage, chromosomal alterations, and other genotoxic endpoints following exposure to aluminium compounds; however, the overall evidence for aluminium-induced genotoxicity remains inconsistent and has been critically questioned (Jenkinson, 2021) [28]. Such effects may arise indirectly through oxidative stress, interference with DNA-associated proteins, altered repair mechanisms, or disturbances in cellular metabolism.

Oxidative damage to DNA can produce modified bases, strand breaks, and other lesions that may compromise genomic integrity. If such damage is not adequately repaired, it may contribute to cellular dysfunction or activation of cell-death pathways. The extent to which aluminium directly interacts with DNA versus producing genotoxicity indirectly through oxidative and metabolic disturbances remains an important area for further investigation.

8. Apoptosis and Other Cell-Death Pathways

When cellular injury becomes sufficiently severe, aluminium exposure may activate programmed cell-death pathways. Experimental studies have reported increased markers of apoptosis following aluminium exposure, including changes in pro- and anti-apoptotic proteins and activation of downstream cell-death signalling (Skalny *et al*., 2021) [47]

Mitochondrial dysfunction and oxidative stress can contribute to apoptosis by altering mitochondrial membrane integrity and promoting activation of caspase-dependent pathways. Similarly, disturbances in intracellular calcium homeostasis may activate calcium-dependent proteases and other pathways associated with cellular injury (Wei *et al*., 2023; Walton, 2012) [54, 55].

Thus, apoptosis may represent a downstream consequence of several upstream mechanisms rather than an independent toxicological event. Persistent oxidative stress, mitochondrial dysfunction, calcium dysregulation, inflammatory signalling, and DNA damage may converge on cell-death pathways, ultimately contributing to tissue injury.

9. Interconnected Mechanisms of Aluminium Toxicity

The mechanisms described above should not be considered as independent events. Aluminium-induced oxidative stress can impair mitochondrial function, while mitochondrial dysfunction can further increase ROS production. Oxidative imbalance may also influence calcium homeostasis, membrane integrity, inflammatory signalling, and DNA stability. Similarly, altered calcium signalling can affect mitochondrial activity and cell-death pathways (Walton, 2012; Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46, 54].

This interconnected mechanism provides a more comprehensive framework for understanding aluminium toxicity. The final biological outcome is likely to depend on the interaction between aluminium speciation, exposure dose and duration, tissue-specific susceptibility, antioxidant capacity, and the ability of the organism to eliminate or sequester aluminium. Consequently, organ-specific toxicity discussed in the following section can be viewed as the result of overlapping molecular disturbances rather than a single mechanism.

Organ-Specific Toxicity of Aluminium

Aluminium-induced toxicity is not restricted to a single organ system. Following absorption and tissue distribution, aluminium may accumulate in organs such as the brain, liver, kidneys, and reproductive tissues, with the severity of injury depending on the dose, chemical form, route, and duration of exposure. The major pathological effects reported in experimental studies include oxidative stress, inflammation, mitochondrial dysfunction, cellular degeneration, and alterations in tissue architecture (Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46]. The major organ-specific effects of aluminium toxicity are summarized in Table 1.

1. Neurotoxicity

The nervous system is considered one of the major targets of aluminium toxicity. Experimental studies have associated aluminium exposure with oxidative stress, neuroinflammation, altered neurotransmission, disturbances in calcium homeostasis, and neuronal degeneration (Klotz *et al*., 2017; Bonfiglio *et al*., 2023) [5, 30].

Aluminium exposure may promote oxidative imbalance in neural tissue by increasing lipid peroxidation and reducing antioxidant defences. Because neurons have high metabolic requirements and relatively limited capacity for regeneration, persistent oxidative stress may contribute to neuronal dysfunction and structural damage (Sieg *et al*., 2019) [46].

Neuroinflammatory responses have also been reported following aluminium exposure. Experimental evidence indicates that aluminium can be associated with activation

of astrocytes and microglia together with increased oxidative stress and inflammatory responses (Akinrinade *et al*., 2015) [3]. Such glial responses may contribute to a sustained inflammatory environment within the nervous system and may further aggravate neuronal injury.

Aluminium exposure has additionally been investigated in relation to pathological changes associated with Alzheimer's disease. Experimental studies have reported alterations in amyloid-β, phosphorylated tau, inflammatory mediators, and oxidative stress following aluminium exposure in animal models (Dey & Singh, 2022) [15]. However, evidence from experimental and epidemiological studies does not establish aluminium exposure as a definitive cause of Alzheimer's disease, and this relationship remains an area of scientific investigation (Klotz *et al*., 2017; Bonfiglio *et al*., 2023) [5, 30].

Structural alterations have also been reported in the hippocampus and other brain regions following experimental aluminium exposure. Changes in neuronal morphology and neuronal density have been observed in dose-dependent experimental studies, suggesting that prolonged exposure can produce measurable neuroanatomical alterations (Massand *et al*., 2022).

Overall, the available evidence suggests that aluminium-associated neurotoxicity may arise through the combined effects of oxidative stress, neuroinflammation, altered calcium signalling, and neuronal degeneration rather than through a single pathological pathway.

2. Hepatotoxicity

The liver is an important organ in aluminium disposition and may accumulate aluminium following prolonged exposure. Experimental studies have demonstrated biochemical and histopathological alterations in the liver following exposure to different aluminium compounds and doses (Klotz *et al*., 2017; Sieg *et al*., 2019) [30, 46].

Aluminium-induced hepatic injury has frequently been associated with oxidative stress. Increased lipid peroxidation together with alterations in antioxidant defence may impair hepatocellular membrane integrity and contribute to cellular injury. Experimental exposure has also been associated with alterations in serum biochemical markers of hepatic function, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

A recent study in Wistar rats reported increases in ALT, AST, and ALP together with alterations in hepatic phospholipid and cholesterol profiles following repeated aluminium chloride exposure. Histopathological examination further demonstrated structural alterations in the liver, supporting the presence of aluminium-associated hepatic injury (Shahabuddin *et al*., 2024) [20].

Similar findings have been reported following aluminium nitrate exposure. Histopathological changes in the liver of female Wistar rats following repeated exposure to aluminium nitrate, further supporting the susceptibility of hepatic tissue to aluminium-induced injury (Afolabi *et al*., 2020) [1].

The hepatic effects of aluminium may therefore involve an interaction between aluminium accumulation, oxidative stress, altered lipid metabolism, and structural damage. However, differences in aluminium compound, dose, route of administration, and exposure duration should be considered when comparing findings across experimental studies.

3. Nephrotoxicity

The kidneys play a major role in the elimination of absorbed aluminium and are therefore particularly relevant to aluminium toxicokinetics. Prolonged exposure may increase aluminium retention and place additional stress on renal tissue, particularly when renal clearance is compromised (Klotz *et al*., 2017; Yokel & McNamara, 2001) [30, 61].

Experimental studies have reported oxidative stress and structural alterations in renal tissue following aluminium exposure. Increased aluminium accumulation in renal tissue together with reductions in antioxidant enzyme activity and increases in oxidative stress markers following repeated aluminium chloride exposure in rats (El-Demerdash *et al*., 2020) [18]. Histopathological examination also demonstrated alterations involving renal tubules and glomerular structures.

The development of renal injury may be related to the interaction between aluminium accumulation and oxidative stress. Increased ROS generation can promote lipid peroxidation and damage cellular membranes, while prolonged oxidative injury may interfere with normal tubular and glomerular function.

An important feature of aluminium nephrotoxicity is the relationship between exposure and elimination. Because renal excretion contributes substantially to aluminium clearance, impaired kidney function may increase systemic aluminium retention and potentially create a feedback loop in which reduced elimination increases aluminium burden. This consideration is particularly relevant to individuals with pre-existing renal dysfunction (Yokel & McNamara, 2001; Klotz *et al*., 2017) [30, 61].

4. Reproductive Toxicity

The reproductive system may also be affected by aluminium exposure. Experimental studies have reported alterations in testicular structure, sperm characteristics, oxidative status, and reproductive function following exposure to aluminium compounds (Yokel, 2020) [60].

Oxidative stress appears to be an important component of aluminium-associated reproductive injury. Testicular tissue is particularly sensitive to oxidative imbalance because developing germ cells and spermatozoa contain membranes rich in polyunsaturated fatty acids that are susceptible to lipid peroxidation. Aluminium-induced oxidative stress may therefore interfere with spermatogenesis and sperm function (Yokel, 2020) [60].

Experimental exposure to aluminium chloride has been associated with changes in reproductive parameters and increased markers of oxidative and apoptotic injury in testicular tissue (Geetha & Jain, 2017) [22]. These findings suggest that prolonged aluminium exposure may affect both the structural integrity of reproductive tissues and the functional processes required for normal spermatogenesis.

Female reproductive tissues may also be susceptible to aluminium exposure. (Ghosh *et al*., 2021) [24] reported ovarian abnormalities following repeated aluminium exposure in an experimental model involving aluminium and ethanol co-exposure. Because ethanol was included as a co-exposure, these findings should not be interpreted as evidence for aluminium acting independently.

Taken together, experimental findings suggest potential reproductive toxicity following aluminium exposure, although differences in sex, dose, aluminium compound,

exposure route, and co-exposures limit direct comparison between studies.

5. Skeletal Effects

Bone represents an important long-term site of aluminium retention. Because aluminium can remain associated with bone tissue for prolonged periods, skeletal tissue may contribute to the overall body burden of aluminium (Klotz *et al*., 2017; Yokel & McNamara, 2001) [30, 61].

Aluminium accumulation has been associated with disturbances in bone mineralization and skeletal metabolism, particularly in conditions involving prolonged exposure or impaired renal function (Klotz *et al*., 2017) [30]. Aluminium may interfere with mineralization processes and with cellular pathways involved in bone formation and remodelling.

The skeletal effects of aluminium are particularly relevant in individuals with reduced renal aluminium clearance, in whom prolonged retention can increase tissue burden. Nevertheless, the severity of skeletal effects depends on exposure history, renal function, and other factors influencing bone metabolism.

6. Thyroid Effects

Experimental evidence also suggests that aluminium exposure may influence thyroid function. In a rat study, repeated exposure to aluminium lactate was associated with reduced thyroidal uptake of radioactive iodine and decreases in circulating T3 and T4 concentrations, together with increased oxidative stress markers (Orihuela, 2011) [39].

However, the findings were not uniform across all thyroid-related parameters, as free T4 and TSH were not significantly altered in the same experimental study. Therefore, the available evidence is more appropriately interpreted as indicating potential thyroid effects rather than establishing a definitive pattern of aluminium-induced thyroid toxicity.

Further studies using standardized exposure conditions and comprehensive thyroid-function assessments are required to clarify whether aluminium produces clinically meaningful alterations in thyroid physiology.

7. Pulmonary Effects

The respiratory system can be directly exposed to aluminium-containing particles, particularly in occupational settings involving mining, smelting, welding, and aluminium processing. The resulting biological effects depend strongly on particle size, chemical composition, concentration, and duration of exposure (Wesdock & Arnold, 2014; Hadrup *et al*., 2024) [25, 56].

Occupational and experimental studies have associated exposure to aluminium-containing dust and particles with pulmonary inflammation and other respiratory alterations. Persistent deposition of certain aluminium-containing materials within pulmonary tissue may contribute to chronic local responses under sufficiently intense or prolonged exposure conditions (Hadrup *et al*., 2024; Dekali *et al*., 2022) [13, 25].

Importantly, occupational exposure often involves complex mixtures rather than pure aluminium. Consequently, pulmonary effects observed in industrial workers cannot always be attributed exclusively to aluminium, because other metals, combustion products, and airborne contaminants may contribute to the observed outcomes (Hadrup *et al*., 2024) [25].

Overall, pulmonary toxicity appears to be particularly relevant to occupational inhalation exposure, whereas its significance for typical environmental exposure requires further clarification.

8. Integrated View of Organ-Specific Toxicity

The organ-specific effects described above share several common molecular features, particularly oxidative stress, inflammation, mitochondrial dysfunction, altered signalling, and cellular injury. However, the final toxicological outcome differs according to tissue-specific susceptibility, aluminium distribution, metabolic activity, antioxidant capacity, and the ability of individual organs to eliminate or retain aluminium.

The brain may be particularly vulnerable because of its high metabolic demand and limited regenerative capacity, whereas the liver and kidneys are important because of their roles in aluminium handling and elimination. Reproductive and endocrine tissues may also respond to prolonged exposure through oxidative and signalling disturbances. Thus, aluminium toxicity is best understood as a systemic process in which a common set of molecular mechanisms produces different manifestations according to the characteristics of individual target organs.

Figure: Cellular and molecular mechanisms of Aluminium toxicity

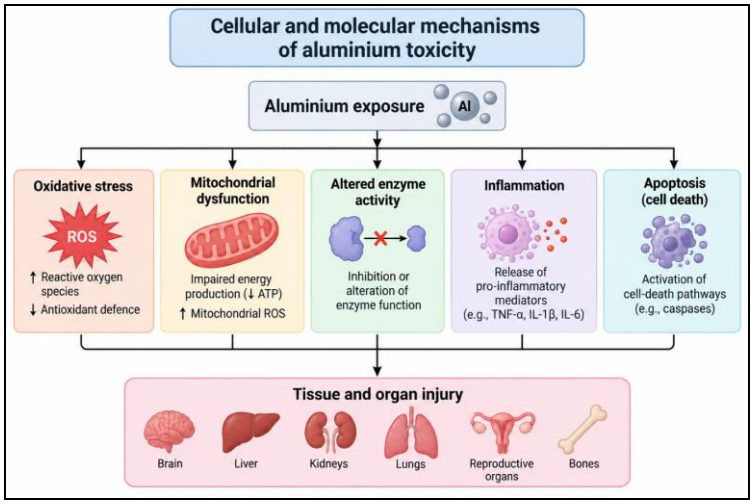


Table 1: Selected experimental studies reporting organ-specific effects of aluminium exposure

References	Target organ/ model organism	Route /dose/ duration	Al compound /key findings
Dey & Singh, 2022 [15]	Brain (Rat)	Oral (20 mg/kg) for 24 weeks	Aluminium chloride: Aluminium chloride increased Aβ1–42, P231-Tau, TNF-α and IL-6, and oxidative-stress markers, while decreasing GSH and catalase levels in brain tissue, indicating neurobiological changes relevant to Alzheimer's disease.
Massand *et al*., 2022	Brain (Rat)	Oral (100 mg/kg, 300 mg/kg) for 30 days	Aluminium chloride: Aluminium chloride reduced neuronal counts across examined brain regions and produced significant neurodegenerative changes in the CA1 and CA3 hippocampal regions in a dose-dependent manner.
Cui *et al*., 2012 [11]	Brain (Rat)	Oral via drinking water; 0, 2000, 4000 and 6000 mg/L $AlCl_3$ for 90 days	Aluminium chloride: Aluminium levels increased in blood and brain tissue, accompanied by alterations in the Ras/Raf/ERK signalling pathway, including reduced expression of Ras, Raf1, ERK2 and CREB. These changes were associated with impaired learning and memory.
Shahabuddin *et al*., 2024 [20]	Liver (Rats)	Oral (25,35,45 and 55 mg/kg/day) for 30 days	Aluminium chloride: Aluminium chloride increased serum ALT, AST and ALP levels and altered phospholipid and cholesterol levels. Histopathological examination revealed enlarged sinusoidal spaces, loss of distinct hepatic cell boundaries, hepatic cord disorganization, sinusoidal congestion and hepatocyte degeneration.
Afolabi *et al*., 2020 [1]	Liver (Rat)	Oral (32.5 mg/kg/day for 21 days)	Aluminium nitrate: Aluminium nitrate caused marked histopathological alterations, including haemorrhagic areas, hepatic vascular congestion, sinusoidal dilation, inflammatory-cell infiltration, hepatocellular degeneration and necrosis.
El-Demerdash *et al*., 2020 [18]	Kidney (Rat)	Oral (34 mg/kg/alternate day) for 30 days	Aluminium chloride: Aluminium chloride decreased antioxidant enzyme activities (SOD, CAT, GPx, GR and GST), increased TBARS and H_2O_2 levels, and increased aluminium accumulation. Serum HDL-C, total protein, albumin and globulin decreased, whereas triglycerides, cholesterol, LDL-C, urea and creatinine increased. Histopathological examination revealed renal tubular and glomerular alterations.
Geetha & Jain, 2017 [22]	Testis and sperm	Intraperitoneal (10 mg/kg/day) for 28 days	Aluminium chloride: Aluminium chloride decreased testicular weight, plasma testosterone and luteinizing hormone levels, sperm count, motility, morphology and viability, as well as germinal epithelial thickness and seminiferous tubule diameter. It increased seminiferous tubular lumen diameter, TUNEL-positive cells and MDA levels.
Ghosh *et al*., 2021 [24]	Ovary (Rat)	Intraperitoneal Aluminium with ethanol co-exposure (4.2mg/kg/day) for 12 weeks.	Aluminium exposure with ethanol co-exposure produced ovarian abnormalities, including large atretic follicles, oocyte degeneration and vacuolization, and rupture of the zona pellucida.
Orihuela, 2011 [39]	Thyroid gland (Rat)	Intraperitoneal (7mg/kg/day) for 6 weeks	Aluminium lactate: Aluminium lactate reduced thyroidal ^{125}I uptake and decreased T3 and T4 levels, while free T4 and TSH remained unchanged. Thyroidal TBARS levels were also increased.

Critical Analysis, Evidence Gaps and Future Research Directions

Although a substantial body of experimental and observational research has examined aluminium toxicity, important uncertainties remain regarding the relationship between exposure, internal aluminium burden, and adverse health outcomes. Much of the available evidence is derived from animal experiments using relatively high doses of specific aluminium salts, particularly aluminium chloride. Such studies are valuable for identifying potential mechanisms and target organs, but their findings cannot always be directly extrapolated to typical human environmental exposure.

1. Limitations in Exposure Assessment

One of the major limitations in the current literature is the considerable variation in aluminium exposure conditions. Experimental studies differ in the aluminium compound used, dose, route of administration, exposure frequency, and duration. These differences can substantially influence aluminium absorption, tissue distribution, and toxicity. Consequently, apparently conflicting findings between studies may partly reflect differences in exposure conditions rather than genuine biological inconsistencies.

Another important consideration is the distinction between administered dose and biologically available aluminium. The same nominal dose may produce different internal aluminium burdens depending on the chemical form, solubility, ligand interactions, route of administration, and physiological conditions. Therefore, future toxicological studies should, where feasible, combine administered-dose information with measurements of aluminium concentrations in blood and relevant tissues.

2. Translational Limitations of Animal Studies

Animal models have provided important evidence concerning the molecular mechanisms and organ-specific effects of aluminium exposure. However, differences in metabolism, aluminium handling, exposure patterns, and tissue susceptibility between experimental animals and humans limit direct extrapolation of some findings (DeVoto & Yokel, 1994; Klotz *et al*., 2017) [14, 30].

A further concern is that several experimental studies employ doses and administration routes that do not closely

resemble common human exposure scenarios. For example, repeated oral or intraperitoneal administration of aluminium salts at relatively high doses may produce tissue concentrations that are difficult to compare with those resulting from ordinary dietary or environmental exposure. Therefore, dose selection should be accompanied by consideration of human exposure relevance.

Future studies should increasingly incorporate exposure scenarios that better approximate realistic human exposure, including lower doses, longer exposure durations, and environmentally relevant aluminium species. Measurement of internal aluminium burden would further improve the translational value of such experiments.

3. Importance of Aluminium Speciation

Aluminium toxicity cannot be interpreted solely on the basis of total aluminium concentration. Aluminium exists in different chemical forms depending on pH, ligand availability, and the surrounding chemical environment. These species may differ in solubility, bioavailability, tissue distribution, and biological activity (Klotz *et al*., 2017; Yokel, 2000) [30, 57].

A considerable proportion of experimental research has focused on aluminium chloride or other soluble aluminium salts. Although these models are useful for investigating mechanisms, they may not represent the behaviour of all aluminium species encountered during environmental or occupational exposure. Future research should therefore provide clearer characterization of the aluminium species used in experimental studies and distinguish between soluble, particulate, and complexed forms whenever possible.

4. Interactions with Other Environmental and Biological Factors

Human exposure to aluminium rarely occurs in isolation. Individuals may simultaneously encounter other metals, particulate matter, dietary factors, pharmaceuticals, and environmental contaminants. Such co-exposures may modify aluminium absorption, distribution, metabolism, or toxicity (DeVoto & Yokel, 1994; Klotz *et al*., 2017) [14, 30].

Dietary components are particularly relevant because compounds such as citrate and phosphate can modify gastrointestinal aluminium absorption. Similarly, mineral status and physiological conditions may influence aluminium disposition (DeVoto & Yokel, 1994; Klotz *et al*., 2017) [14, 30]. These interactions indicate that individual susceptibility to aluminium may vary considerably even when external exposure levels are similar.

Future studies should therefore move beyond single-agent exposure models where appropriate and investigate environmentally relevant combinations of aluminium with other common co-exposures. Such approaches may provide a more realistic understanding of aluminium-associated health risks.

5. Need for Better Human Evidence

Although experimental studies provide strong evidence that aluminium can produce biochemical and structural changes under defined conditions, establishing the health significance of these findings in humans remains more challenging. Human studies are often affected by difficulties in accurately estimating long-term exposure, differences in individual aluminium metabolism, co-exposures, and the long latency of some potential outcomes (Priest, 2004; Klotz *et al*., 2017) [30, 41].

Biomonitoring can provide useful information about internal aluminium exposure, particularly through measurements in urine or blood (Hadrup *et al*., 2024) [25]. However, a biomarker concentration at a single time point may not necessarily represent cumulative tissue exposure, especially because aluminium has different retention and elimination patterns across tissues.

Longitudinal studies combining repeated exposure assessment with biological monitoring and clinically relevant outcomes would therefore be valuable. Such studies could help clarify whether observed associations represent transient exposure-related changes or persistent biological effects.

6. Organ-Specific Evidence Remains Uneven

The evidence base is not equally developed for all target organs. Neurotoxicity has received considerable attention, particularly in relation to oxidative stress, neuroinflammation, and neuronal alterations. In contrast, the long-term consequences of environmental aluminium exposure on the liver, kidneys, reproductive system, thyroid, and other organs remain comparatively less well characterized in humans.

Experimental evidence nevertheless indicates that aluminium can affect multiple organ systems through overlapping mechanisms, particularly oxidative stress, mitochondrial dysfunction, altered signalling, inflammation, and apoptosis. The challenge is therefore not simply to identify additional toxicological effects, but to determine which effects are most relevant at realistic exposure levels.

7. Need for Mechanistic Integration

A major gap in the current literature is the tendency to investigate individual mechanisms separately. Oxidative stress, mitochondrial dysfunction, calcium dysregulation, inflammation, DNA damage, and apoptosis are often reported as distinct endpoints. In reality, these processes are interconnected and may form a self-amplifying network of cellular injury.

Future research should therefore adopt integrated mechanistic approaches that examine multiple pathways simultaneously. Combining biochemical, molecular, histopathological, and tissue aluminium measurements could provide a more coherent understanding of the progression from exposure to cellular dysfunction and ultimately to organ injury.

8. Recommendations for Future Research

Future investigations should prioritize several areas. First, studies should use well-characterized aluminium species and provide sufficient information regarding dose, route, duration, and exposure conditions. Second, experimental exposure levels should be selected with greater consideration of human relevance. Third, measurements of aluminium in blood and target tissues should be incorporated whenever feasible to distinguish administered dose from internal exposure.

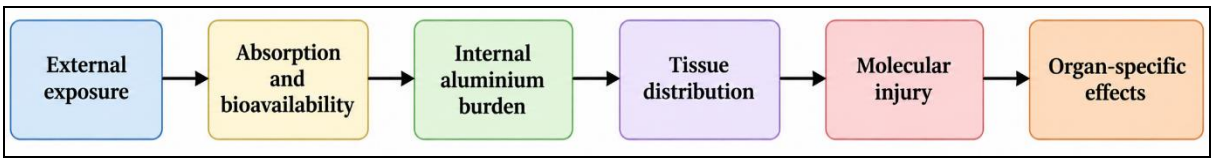
Fourth, greater emphasis should be placed on longitudinal and mechanistic studies that examine the relationship between aluminium accumulation and progressive cellular injury. Finally, human epidemiological and biomonitoring studies should be strengthened to determine whether mechanisms demonstrated experimentally translate into clinically meaningful outcomes.

Overall, the current evidence supports the biological potential of aluminium to induce oxidative, inflammatory, metabolic, and structural disturbances in several organs. However, the magnitude of risk associated with typical human exposure remains dependent on exposure form, dose, duration, individual susceptibility, and internal aluminium burden. Future research should therefore focus not only on demonstrating that aluminium can cause toxicity, but also on determining under what exposure conditions these effects become biologically and clinically significant.

9. Overall Critical Perspective

Taken together, the available literature indicates that aluminium toxicity is biologically plausible and mechanistically complex, but the strength of evidence varies substantially among exposure scenarios and health outcomes. Experimental studies provide consistent support for oxidative stress and cellular injury at sufficiently high or prolonged exposure, whereas evidence linking typical environmental exposure to specific chronic human diseases is less definitive. This distinction is important when interpreting the toxicological significance of aluminium.

A more integrated risk assessment should therefore connect findings across experimental and human studies to help reconcile apparently inconsistent results and identify the exposure conditions under which aluminium is most likely to produce adverse biological effects.



Conclusion

Aluminium is a widely distributed environmental element to which humans may be exposed through dietary, occupational, pharmaceutical, consumer, and environmental sources. Following exposure, its absorption and tissue distribution are influenced by chemical speciation, dose, route of exposure, ligand interactions, physiological conditions, and the capacity for renal elimination. Aluminium can accumulate in tissues including the brain, liver, kidneys, bone, and reproductive organs, providing a basis for tissue-specific biological effects.

The available experimental evidence indicates that aluminium toxicity involves interconnected molecular and cellular mechanisms, including oxidative stress, mitochondrial dysfunction, altered calcium homeostasis, membrane and signal-transduction disturbances, inflammation, DNA damage, and activation of cell-death pathways. These mechanisms may operate simultaneously and can produce different pathological outcomes depending on the susceptibility and physiological characteristics of individual organs.

However, considerable heterogeneity exists among experimental studies with respect to aluminium compounds, doses, routes of administration, and exposure durations. Therefore, findings obtained from high-dose animal models should be interpreted cautiously when considering typical human environmental exposure. In particular, the evidence linking environmental aluminium exposure with specific chronic human diseases remains less definitive than the experimental evidence demonstrating cellular and organ-level toxicity.

Future research should place greater emphasis on realistic exposure scenarios, accurate characterization of aluminium species, measurement of internal aluminium burden, long-term studies, and integration of molecular, biochemical, histopathological, and epidemiological evidence. A better understanding of the relationship between external exposure, aluminium bioavailability, tissue accumulation, molecular injury, and organ-specific effects will be essential for improving assessment of the potential health risks associated with aluminium exposure.

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